The Patent Office

The Patent Office
Cardiff Road
Newport
Gwent
NP9 1RH

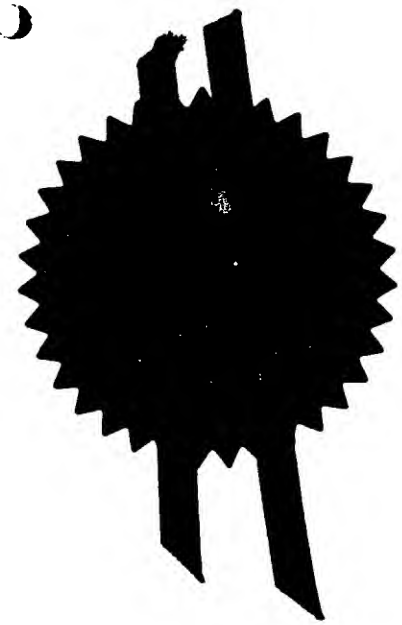
I, the undersigned, being an officer duly authorised in accordance with Section 62(3) of the Patents and Designs Act 1907, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the Patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or the inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

PRIORITY DOCUMENT



Signed A.W. Russell

Dated -3 NOV 1993

For o[illegible] ise

THE PATENT OFFICE 15 JAN 1993 RECEIVED BY HAND

19JAN'93 H00258250 PAT 1.77 UC 25.00

15 JAN 1993

Your reference 70/4243/01

9300753.1

Notes
Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071–438 4700).

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

❶ Title of invention

1 Please give the title of the invention: CHEMICAL COMPOUND

❷ Applicant's details

❷ Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

❑ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name: Leo Pharmaceutical Products Ltd. A/S (Løvens Kemiske Fabrik Produktionsaktieseksab)

Country *(and State of incorporation, if appropriate)*: Denmark

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases**, please give the following details:

Address: Industriparken 55
DK-2750 Ballerup

UK postcode *(if applicable)*

Country: Denmark

ADP number *(if known)*: 5683290001

Warning
After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977 and will inform the applicant if such prohibition or restriction is necessary. Applicants resident in the United Kingdom are also reminded that under Section 23, applications may not be filed abroad without written permission unless an application has been filed not less than 6 weeks previously in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction revoked.

2d, 2e and 2f: If there are further applicants please provide details on a separate sheet of paper.

❑ **Second applicant** ***(if any)***

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2f **In all cases**, please give the following details:

Address

UK postcode *(if applicable)*

Country

ADP number *(if known)*

❶ *An address for service in the United Kingdom must be supplied*

Please mark correct box

❶ Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ➡ ***go to 3b***

⬇ ***please give details below***

Agent's name GILL JENNINGS & EVERY

Agent's address Broadgate House
7 Eldon Street
London

Postcode EC2M 7LH

Agent's ADP number 745002

3b: *If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.*

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

Address

Postcode

Daytime telephone number *(if available)*

ADP number *(if known)*

❹ Reference number

4 Agent's or applicant's reference number *(if applicable)* 70/4243/01

❺ Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ ***go to 6***

↓ ***please give details below***

❑ number of earlier application or patent number

❑ filing date

(day month year)

❑ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

❻ Declaration of priority

❻ If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day, month, year)*

❼ *The answer must be 'No' if:*
- *any applicant is not an inventor*
- *there is an inventor who is not an applicant,* ***or***
- *any applicant is a corporate body.*

❼ Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inv s

Please mark correct box

Yes [ ] No [X] ➡ ***A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).***

❽ *Please supply duplicates of claim(s), abstract, description and drawing(s).*

❽ Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			
Claim(s)		Description	4
Abstract		Drawing(s)	

8b Which of the following documents also accompanies the application?

Please mark correct box(es)

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 – Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 – Preliminary Examination/Search	
Patents Form 10/77 – Request for Substantive Examination	

❾ *You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.*

❾ Request

I/We request the grant of a patent on the basis of this application.

GILL JENNINGS & EVERY
Agents for the Applicants

Please sign here ➡ Signed [signature] Date 15. 01. 93 (day month year)

R E Perry

A completed fee sheet should preferably accompany the fee.

Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to either:

❑ ***The Comptroller***
The Patent Office
Cardiff Road
Newport
Gwent
NP9 1RH

or

❑ ***The Comptroller***
The Patent Office
25 Southampton Buildings
London
WC2A 1AY

CHEMICAL COMPOUND

The present invention relates to calcipotriol, hydrate - a new crystalline form of calcipotriol - with superior technical properties e.g. in the manufacture of crystal suspension formulations.

Calcipotriol (INN) (calcipotriene (USAN), (1α,3β,5Z,7E,22E,24S)-24-Cyclopropyl-9,10-secochola-5,7,-10(19),22-tetraene-1,3,24-triol) is described in International patent application No. PCT/DK86/00081, filing date 14th July 1986, publication No. WO 87/00834.

Calcipotriol possesses a remarkable profile of biological activity which has proved very useful e.g. in the topical treatment of psoriasis.

Due to the poor stability of calcipotriol in certain solutions it is in some formulations, in particular in creams and gels, preferred to use crystal suspensions.

In order to prepare suitable crystal suspension formulations it is mandatory to be able to control the crystal size, this parameter being important with regard to obtaining a reproducible release of the active compound from the formulation. The crystalline bulk drug is usually subjected to micronization or to a wet milling process in order to reduce the crystal size before the final suspension formulation is prepared.

In the case of calcipotriol a wet ball milling process has been used. However, it has turned out to be technically difficult to perform this process when using the anhydrous crystal form described in WO 87/00834. These crystals are not easily wetted and during the milling process they develop a stable foam which results in difficulties in obtaining a suitable small and uniform particle size.

It has now surprisingly been found that these technical problems can be avoided when a hitherto unknown crystalline form of calcipotriol, i.e. calcipotriol, hydrate, is used instead of the known anhydrous form. The hydrate is

technically superior to the anhydrate; it is easily wetted and the wet ball milling process is running smoothly.

This novel product is the monohydrate of calcipotriol which is perfectly crystalline, stable and well suited for its use in modern therapy.

Calcipotriol, monohydrate may be prepared by dissolving crystalline or non-crystalline calcipotriol in an organic solvent, e.g. ethyl acetate or acetone, followed by the addition of water and optionally a non polar solvent, e.g. hexane.

Example 1

Calcipotriol (2.5 g) was dissolved in ethyl acetate (80 ml) at 50-80°C and filtered. The solution was saturated with water, and the product precipitated upon voluntary cooling to room temperature. The resulting slurry was cooled to 0-10°C and filtered. The filtered product was dried in vacuo to give calcipotriol, hydrate (2.35 g).

IR spectroscopy KBr technique

Lines characteristic for the hydrate are 1455 (m), 1442 (m), 1330 (w), 1290 (m), 1210 (m), 1085 (m), 907 (m), 895 (m) and 573 (w) cm^{-1}, respectively.

Solid state CPMAS[1] NMR

The following resonances are characteristic for calcipotriol, hydrate: 147.9, 146.5, 134.8, 130.3, 129.0, 126.5, 116.0, 109.4, 75.5, 68.2, 67.2, 56.9, 55.2, 47.8, 47.5, 42.9, 42.0, 41.3, 30.7, 28.9, 25.6, 23.1, 22.6, 19.5, 14.6, 6.2 and 1.9 ppm, respectively.

Differential Scanning Calorimetry (DSC)

On a Perkin Elmer DSC7 instrument using 20°C/min. and approx. 2 mg sample, the hydrate shows loss of water near 117°C and a melting peak near 169.7°C.

---

1 Cross Polarization Magic Angle Spinning

ene glycol in water at 75°C and mix the solution with the fatty phase. Homogenize the emulsion and cool to 30°C. Mill calcipotriol, hydrate in part of the aqueous phase to a particle size predominantly below 10 µm and suspend in an aqueous solution of disodiumhydrogenphosphate and chloroallylhexaminiumchloride. Add the suspension to the emulsion and fill the cream in tubes.

Example 2

Calcipotriol (22.7 g) was dissolved in methanol (200-250 ml), filtered and concentrated in vacuo to a residue which was dissolved in ethyl acetate (200-250 ml) at 50-80°C and water (2 ml) was added. The resulting solution was seeded with calcipotriol, hydrate, and the product precipitated upon voluntary cooling to room temperature. Hexane (100 ml) was added from a dropping funnel, the resulting slurry was cooled to 0-10°C and filtered.

The filtered product was washed with a 1:1 mixture of ethyl acetate and hexane (200 ml) and dried in vacuo to give calcipotriol, hydrate (19.7 g), shown to be identical with the products described in Example 1.

Example 3

Calcipotriol (120 mg) was dissolved in acetone (2 ml) and water (1.5-3 ml) was added. The product crystallized spontaneously and the resulting slurry was cooled to 0-10°C and filtered. The filtered product was dried in vacuo to yield calcipotriol, hydrate (100 mg), shown to be identical with the product of Example 1.

Example 4

Cream 50 µg/g

Calcipotriol, hydrate	50 mg
Cetomacrogol 1000	30 g
Cetostearylalcohol	60 g
Chloroallylhexaminium chloride	0.5 g
Propyleneglycol	30 g
Disodiumhydrogenphosphate	2 g
Liquid paraffin	50 g
White soft paraffin	170 g
Purified water ..... up to	1000 g

Melt cetomacrogol 1000, cetostearylalcohol, liquid paraffin and white soft paraffin at 75°C. Dissolve propyl-